ORIGINAL ARTICLE

Mycobacterium tuberculosis at autopsy—exposure and protection: an old adversary revisited

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Background: The risk of encountering tuberculosis (TB) has reduced with the decreased incidence of the disease; however, it still can be found at autopsy.
Aim: To assess the magnitude of exposure to *Mycobacterium tuberculosis* at autopsy in a large general hospital setting, in a country with low incidence.
Methods: Retrospective search of the autopsy records from 1991 to 2004. Patients' records and histological slides were reviewed, and medical personnel interviewed.
Results: 15 cases of active TB were identified in the 14-year period, during which 4930 autopsies were performed (1 case per 329 autopsies); of these, 10 cases were unsuspected (67%). Five of these cases contained abundant acid-fast bacilli. Patients tended to be middle aged and males with complex clinical histories; two were HIV positive. Two patients were brought in dead to hospital, with no clinical indication of TB. Of 15 autopsy staff, 1 required chemoprophylaxis but none contracted TB.
Conclusion: The risk of unexpectedly encountering TB at autopsy continues even in a low-risk European setting. It has implications for the health of autopsy room staff, autopsy room design and ventilation, choice of protective equipment and for the public health service. Protective strategies include assessment of the risk of a case being infected, early recognition of gross lesions, use of methods for reducing the production of infected aerosols and protection against any aerosols created.

The risks of transmission of *Mycobacterium tuberculosis* to pathologists have long been known; at the beginning of the 19th century, René Laennec, the inventor of the stethoscope, attributed his infection to sawing through tuberculous vertebrae.[1] Early 20th-century descriptions of cutaneous inoculation of tuberculosis (TB) in autopsy staff used terms such as ''prosector's wart'' or ''anatomical tubercule''[2 3] to define a form of TB almost exclusively occupationally acquired. There are numerous reports of pathologists, autopsy staff and medical students acquiring pulmonary TB at autopsy.[4–13] The occupational risk of TB for the staff of laboratories and postmortem rooms is estimated to be 100–200 times that of the general public.[14] A survey of hospital staff in the 1980s[15] recorded an incidence (per 100 000 staff) of 9.4 cases of TB among laboratory and mortuary staff and 0.6 cases among clerical and administrative staff. The greater risk to autopsy staff than to clinical staff is illustrated by a report[16] where undiagnosed pulmonary TB led to the skin test conversion of 5 autopsy personnel, but none of the 40 clinical workers who cared for the infected patient over a prolonged period. In a similar study at a medical examiner's office,[4] 5 of 18 employees, including secretarial staff in offices adjacent to the autopsy room, had tuberculin skin test conversion and 2 became infected with the resistant organism after autopsies were performed on patients with multidrug-resistant TB.

In 1990, the World Health Organization stated that one-third of the world's population (1.7 billion people) were infected with *M tuberculosis*.[17] Of the 8.5 million new cases that occurred in 2000, 9% were in the HIV-positive population, 3.2% had multidrug-resistant TB and there were 1.8 million deaths.[18] Elderly people are 20 times more likely to have the diagnosis at autopsy.[19] However, this age profile may reverse with the re-emergence of TB in the HIV-infected population, together with the advent of multidrug-resistant TB,[20 21] which has again focused attention on the risk of infection to pathologists and autopsy staff.

The aim of this study was to determine the magnitude and pattern of exposure of autopsy personnel to TB in the autopsy room in a low-incidence setting, and to review this pattern in relation to the likely protective effect of current preventive strategies.

METHODS

The hospital autopsy records for the years 1991 to 2004 inclusive were retrospectively studied. Age, sex, ethnic origin, immigrant status, background clinical history (including HIV status), cause of death, length of stay in hospital, results of microbiological cultures and type of TB diagnosed at autopsy were recorded.

During most of the period, autopsies were performed in a facility with an enclosed ''high-risk'' room and a larger open-plan room with three tables. There was downdraft negative-pressure ventilation in the enclosed room and general ventilation with extraction through filters in the larger room. The rooms used for individual autopsies were not recorded, but most cases undiagnosed before autopsy were carried out in the larger room. For most of the period, effective respiratory protection was not available. A new facility with three single rooms opened in 2002.

Reappraisal of the H&E slides and corresponding Ziehl-Neelsen (ZN) stains was carried out to confirm the diagnosis and to quantify acid-fast bacilli (AFB). These were semi-quantitatively assigned to four groups based on the number of AFB per high-power field (AFB/HPF): 0, negative; +1, weak positivity (0–50 AFB/HPF); +2, moderate positivity (50–100 AFB/HPF); and +3, strong positivity (>100 AFP/HPF). HPF was taken at a magnification of ×40 (fig 1).

Autopsy personnel listed in the records were interviewed to assess whether they used respiratory protection during the

Abbreviations: AFB, acid-fast bacilli; AFB/HPF, acid-fast bacilli per high power field; TB, tuberculosis; ZN, Ziehl-Neelsen

Table 1 Features of 15 cases of tuberculosis found at autopsy

Year	Age	Sex	Clinical history	Type of TB	ZN stain	Cause of death	Hospital stay (days)	Microbiology: culture specimen	Microbiology: Smear	Microbiology: Organism
1992	85	F	Congestive cardiac failure, pneumonia, ischaemic cardiomyopathy	Lung cavitating	+1	TB pneumonia	74	Lung	+	MTB
1992	66	M	Suspected farmer's lung, hypertension, PUO	Miliary	+1	Miliary TB	3	Liver	+	
1993	63	M	Ischaemic cardiomyopathy hypertension, nephrotic syndrome, CXR opacity	Miliary	+1	Cardiomyopathy	56	Not done		
1994	72	M	Atrial fibrillation, burns, pneumonia,	Lung-	+3	Sepsis	>20	Lung		
			Left-ventricular failure	Upper lobe fibrosis, subpleural nodule		Burns		Blood	−	
								Wound		
1994*	56	M	Epilepsy, personality disorder, pneumectomy (non-small cell carcinoma)	Lung-caseating nodules	+1	Sepsis	>10	Blood	−	NG
								Chest drain	−	NG
								Lung	+	MTB
			Pulmonary TB							
			Treated 1991 for 6 months (R, I, E, P)							
			Relapse 1993 treated for 9 months,							
			? Medication							
1995	73	M	Ischaemic cardiomyopathy, ethanol misuse, PUO, collapse	Miliary	+1	Cardiomyopathy	17	Not done		
1995	85	M	Abdominal pain, BID	Miliary	+2	Pulmonary Embolism	0	Not done		
1996*	67	M	Rheumatoid arthritis (taking steroids) ischaemic heart disease, hypertension, peptic ulcer, pulmonary fibrosis Pulmonary TB: treated 9 days with R, I, E, P	Miliary	+3	Sepsis	11	Pancreatic abscess	+	NG
1998	57	M	Metastatic lung adenocarcinoma	Miliary	+2	Carcinoma	5	Pericardial fluid	−	NG
1998†	54	M	BID	Miliary	+3	Miliary TB	0	Ascitic fluid	+	NG
								Mesenteric nodule	+	MTB
1999	65	M	Haemopytsis	Renal	+1	Lobar pneumonia	<1	Kidney	−	NG
2000*	41	M	Fall, HCV+, HIV+, TB, lymphoma	Miliary	+1	Haemorrhage from splenic laceration	<1	Not done		
			Treatment for TB not known							
2000*	66	M	Sepsis, TB	Miliary	+1	Sepsis	19	Ascitic fluid		
			Pulmonary TB: treated 17 days with R, I, E, P					Catheter tip		
2002*	35	F	TB, HIV+, malaria, ITP	Lung-caseating nodules	−	Cerebral	6	Bone marrow		
			African immigrant			Haemorrhage		Blood culture	−	
			3 months partial treatment for pulmonary TB, ? medication			ITP		Urine		
2004	40	M	Treated 2000, TB, cirrhosis	Lung	0	Bronchopneumonia	0	Lung	+	MTB

AFB, acid-fast bacilli; BID, brought in dead; CXR, chest *x* ray; E, ethambutol; F, female; I, isoniazid; HCV, hepatitis C virus; ITP, immune thrombocytopenia; M, male; MTB, *Mycobacterium tuberculosis*; NG, no growth; P, pyrazinamide; PUO, pyrexia of unknown origin; R, rifampin; S, streptomycin; TB, tuberculosis; ZN, Ziehl-Neelsen.

*Known cases of TB.

autopsy, had a previous BCG, follow-up Mantoux, chest *x* ray and prophylactic treatment. Ethical approval was obtained from the hospital's research ethics committee.

RESULTS

There were 15 cases of active TB in the 14-year period, during which 4930 autopsies were carried out (1 case/329 autopsies; table 1). Ten cases were of unsuspected TB (67% of the total cases of TB), of which seven were miliary TB, two were pulmonary and one renal. Six of the seven cases of miliary TB involved the lung. A total of 5 of 10 (50%) of the unsuspected cases had abundant microorganisms: a +2 or +3 score for AFB with ZN staining. By contrast, there were low numbers of AFB (1+) in 4 of 5 suspected cases, probably as a result of treatment for TB (one previously diagnosed case had necrotising granulomas but a negative ZN stain). During 1993–2004, 339 patients were diagnosed as having TB in our institution that serves a population of 300 000 people. Eight cases of unsuspected TB were diagnosed at autopsy during this period (2.4% of all diagnosed cases). The number of deaths in the remaining 331 patients is unavailable.

In 40% of the cases, the cause of death was a direct result of TB. The age profile was that of an older population (mean age 63.2 years; 68.7 years in the unsuspected cases vs 49.5 years in known cases). Only two patients were female. Two cases were brought in dead and little history was provided to the prosector, but most (86%) had complex clinical histories. In all, 3 of 10 (30%) of the unsuspected cases were identified first on histological examination; the remainder were established at gross dissection.

In all, 15 personnel (autopsy technicians and pathologists) conducted the autopsies. One had no previous BCG, had a positive Mantoux test on follow-up and required chemoprophylaxis. A large number of AFB (3+) were found on the ZN stain from the autopsy at which exposure occurred (tables 1 and 2).

DISCUSSION

This study indicates that, corresponding to its current lower population incidence in Western Europe, TB is now an unusual finding at autopsy (about 1 case/300 autopsies), but it remains a hazard in the autopsy room. The absence of significant morbidity in this study should not obscure the fact that TB is a serious infection for autopsy personnel. Although unprotected prosectors have a low risk of contracting clinical disease, it is likely that most pathologists, and all pathology technicians, will be exposed to occupationally acquired TB during their professional life, with potentially serious implications. Infection may require increased medical supervision, repeated imaging studies, long-term treatment with possible side effects and is likely to cause anxiety; it may result in difficulties with employment and in obtaining emigration visas. It also has real potential to cause serious illness either in the early period or as a secondary or reactivation disease years later; it may be catastrophic if caused by a multiresistant organism.

Clinically undiagnosed TB makes up a substantial proportion of active TB cases diagnosed at autopsy. The 67% incidence in this study is similar to figures in older studies.[10–28] A total of 70% of cases of active TB were first diagnosed at autopsy in an

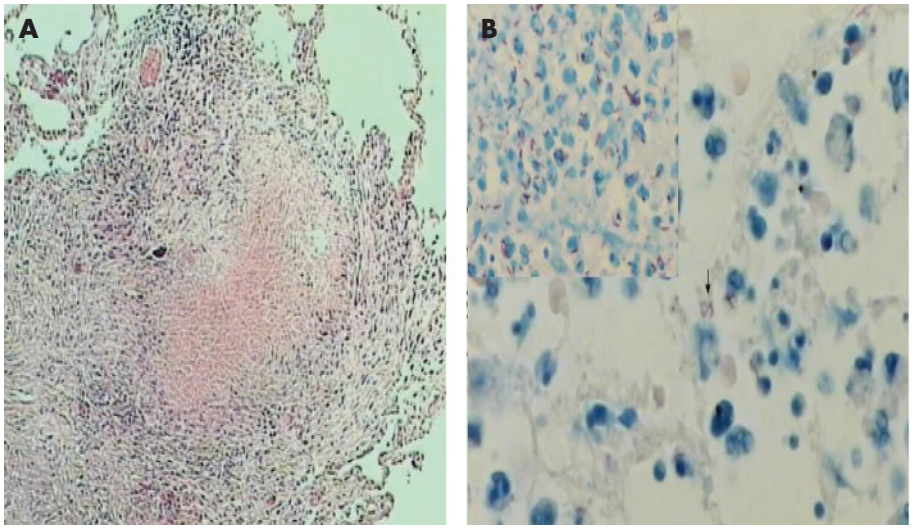

Figure 1 (A) H&E (magnification ×4) stain of a characteristic caseating granuloma found in a tuberculosis autopsy. (B) Zeihl-Neelsen stains (magnification ×40) for acid-fast bacilli from two separate tuberculosis autopsy specimens showing 1+ (arrow; weak) and 3+ (inset; strong) positivity.

Italian study,[29] 44% in a Swiss study[30] and 75% in a Japanese study.[31] A similar study in San Francisco found that 4% of the reported 3102 TB cases were diagnosed after death.[32]

Our results highlight that complex clinical histories may mask the underlying diagnosis of TB. Cancers and a history of recent major operations were two major conditions associated with active TB in a previous study.[33] These were not features in the current series, where only one unsuspected patient had carcinoma; by contrast, five had severe ischaemic heart disease. Other reasons cited for both the inability and delay in diagnosing TB include a low index of clinical suspicion,[34] clinicians' inexperience,[35] symptoms masked by antibiotics,[36] non-specific symptoms,[34] atypical chest *x* ray findings[28] and the increasing prevalence of extrapulmonary TB.[27 31] With the increasing incidence of HIV-associated TB, it is likely that more cases will present at extrapulmonary sites and with both atypical symptoms and non-specific chest *x* ray findings. In our study, two of the suspected cases were HIV positive, with one having miliary TB. Notably, both patients were >20 years younger than the average patient in the study, and one had only recently immigrated to Ireland.

This study contained three categories of subjects: (a) those suspected or diagnosed before autopsy (n = 5); (b) those first suspected or diagnosed during autopsy (n = 7); and (c) those unsuspected until later review of microscopy (n = 3). It is not possible to quantify the degree of exposure without the use of air sampling techniques, but intuitively the number of organisms seen on ZN staining might provide an approximate quantification. The finding of large numbers of organisms in half the unsuspected cases highlights the significant risk to autopsy personnel of acquiring the disease in the absence of protective measures.

Box 1 outlines the available protective strategies for autopsy personnel, applicable to the three categories above. It should be highlighted that for areas where BCG protection is not routinely used, Morbidity and Mortality Weekly Report guidelines,[37] recently updated, suggest that autopsy personnel should have baseline TB screening on hire. Those with negative baseline test results should be screened annually for symptoms and evidence of infection. The recently available interferon gamma release assay tests may serve as a substitute for a skin test in this setting. These in vitro tests are expected to be more specific than tests that use tuberculin-purified protein derivatives.[38]

When TB is unsuspected, early recognition of tuberculous lesions and minimising dissection will minimise aerosols. However, this has become more difficult in modern autopsy practice for several reasons. Prosectors perform fewer autopsies, they are less familiar with the gross appearance of TB because it has now become rare and the learning opportunities of diagnostic and teaching demonstrations on retained organs have virtually ceased because of the organ retention controversy. Previously, if there was even a moderate suspicion of TB, organs were retained for a period (ranging from at least 24 h to weeks) to be sterilised by immersion or perfusion fixation in formalin before dissection.[39] Now, because of the difficulty in obtaining authorisation to retain organs, there is increased pressure to directly dissect suspected tissue, with consequent increased likelihood of infective aerosol production.

Any aerosol produced will be minimised by good autopsy room design and maintenance. Downdraft ventilation takes the infected aerosol away from the prosector's face and extracts it from the floor area; negative pressure ensures that adjacent rooms are not contaminated and sufficient changes of air (12/h) is usually recommended to ensure that any dispersed aerosol is removed quickly. Filters for the externally discharged air must be changed regularly to ensure that the ventilation system continues to be effective. Contamination will be more contained (and easier to disinfect) and ventilation systems

Table 2 Highlights on the occupational follow-up in the immediate aftermath of the autopsy cases

No autopsy personnel	Respirator used	Previous BCG	Follow-up Mantoux	Mantoux positive	Follow-up CXR	Chemoprophylaxis	TB
15	7	14	1*	1	1	1	0

CXR, chest *x* ray; TB, tuberculosis.
*This person had no previous BCG.

Box 1: Tuberculosis at autopsy, safety aspects

1. Awareness/risk assessment of deceased

- Clinical findings or other suspicions of TB
- High-risk group (HIV, steroids, etc)
- History of TB:
  - Sensitive or resistant organism
  - Adequacy of therapy

2. Minimise aerosol creation

- If gross lesions suspected:
  - Minimise dissection
  - Consider retaining organ; fix by perfusion or immersion

3. Reduce any aerosol created

- Ventilation: downdraft, 12 changes/h, negative pressure
- Maintenance: change filters regularly, test ventilation (use smoke test)
- Autopsy room design (enclosed single-table room safer than open plan)

4. Protect personnel

- Be Mantoux positive; if negative take BCG or frequent Mantoux tests
- Personal protective devices: and protection
  - Routine use of N95 mask
  - N95, N99 masks or enclosed ventilators in high-risk/suspect cases
  - Gloves: 2 layers using both latex and neoprene cut-resistant gloves
  - Minimise number in room if TB suspected

5. Sterilise

- Routine disinfection
- Decontaminate autopsy room if TB suspected

6. Monitor health of personnel

- Awareness/ risk assessment of any illness
- Mantoux testing and chest imaging
- Medication, prophylactic or therapeutic

7. Public health

- Notification
- Contact tracing

Take-home messages

- The risk of unexpectedly encountering tuberculosis at autopsy continues even in a low-incidence European setting.
- A total of 15 cases (1/329 autopsies) were identified during 14 years. The majority (67%) were unexpected and contained abundant tubercule bacilli.
- Routine respiratory protection using N95 masks is feasible. Although unprotected prosectors have a low risk of contracting clinical disease, it is likely that most pathologists, and all pathology technicians, will be exposed to occupationally acquired tuberculosis during their professional life, with potentially serious implications.
- Protective strategies include autopsy room design and ventilation, choice of protective equipment, assessment of the risk of a case being infected, early recognition of gross lesions, use of methods of reducing the production of infected aerosol and protection against any aerosol created.

may be easier to regulate in smaller single-table rooms than in larger open-plan multi-table facilities. Systems that are noisy or produce uncomfortable draughts or variable ambient temperature are unsatisfactory and hazardous as they risk being shut down by staff.

No respirator is fully effective, respirators should be relied on only as a secondary means of protection against airborne toxic material after assessment of the possibility of TB.[40] Simple surgical masks have little protective effect. N95 masks (so called because they exclude > 95% of aerosol particles) provide substantial protection and are reported by many autopsy personnel to be comfortable to wear routinely during all autopsies; (standard precautions suggest that they should be worn in all cases). N99 masks (>99.9% exclusion) are more effective at excluding aerosols, but are also more uncomfortable. Enclosed space-suit type masks give absolute protection but are heavy and hot, may produce fogging of visors or eyeglasses and cause difficulty in talking,[40] factors that may lead to increased risk of cut injury or poor performance of the autopsy.

To prevent cutaneous TB, the Royal College of Pathologists Guidelines (http://www.rcpath.org) include recommendations on standard autopsy clothing and appropriate gloves (''double-gloving'' with both latex and neoprene cut-resistant gloves), together with observation of standard precautions.

Older recommendations, that suggested retention and fixation of suspect organs before dissection, have been replaced by recent guidelines (http://www.rcpath.org) which indicate that dissection may continue with the use of respiratory protection. Although intuitively protective this is not evidence based; many pathologists, especially in the large number of facilities with suboptimal ventilation, would recommend organ retention/ fixation (with appropriate consent) before completion of the dissection.

Prolonged stays in hospital with undiagnosed TB can be an important source of the disease for clinical healthcare workers; diagnosis at autopsy may identify this substantial health risk to hospital staff contacts (the average duration of stay in hospital in our study was 18.9 days for unsuspected cases) in addition to contacts in the community before admission. Naalsund *et al*[34] found in their study of TB autopsies between 1977 and 1989 that 96 patients died from active pulmonary TB and that the median length of stay in hospital was 24 days before death in the untreated group, and 21 days before start of treatment in the treated group. An untreated positive patient is infectious for about 2 years on average,[41] during which time a single patient can infect, on average, 20 contacts.[42] Eight patients and two employees at a chronic care facility had a tuberculin skin test conversion that was ultimately traced to a cadaver diagnosed with TB 3 years previously.[43] Two of the patients in our study arrived dead to the accident and emergency department, which presented challenges in contact tracing. These points emphasise

the importance of reporting previously undiagnosed TB to public authorities.

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